requirement of 35 U.S.C. §112, ¶1. The related Preliminary Amendment to the specification stands objected to as new matter under 35 U.S.C. §132. Claims 15-23 stand subjected to restriction and were withdrawn from consideration as being constructively elected under 35 U.S.C. § 1.145.

Applicants respectfully traverse the 102(e) rejection and respectfully request reconsideration of the remaining rejections and objection and the restriction requirement for the reasons set forth below.

REMARKS

Rejections Under §102(e)

The Office Action rejected claims 1-8 and 10-14 as anticipated under § 102(e) by DiNapoli WO 01/51044 A2. Applicants respectfully disagree and traverse the rejection because DiNapoli does not anticipate Applicants' discovery that administering rhein and/or diacerein to patients will treat an underlying cause of the claimed pathological conditions, and that the further effect of the treatment of an underlying cause of the claimed pathological conditions will be to minimize or prevent the need for surgery to treat them.

The Office Action rejected claims 1-8 and 10-14 as anticipated by DiNapoli because it discloses the employment of diacerein and rhein in an oral dosage form for the treatment of psoriatic arthritis (PA), osteoarthritis (OA) and rheumatoid arthritis (RA), and that diacerein and rhein are known to inhibit the production of IL-1 and TNF-α production. However, Applicants respectfully disagree that DiNapoli teaches the full breadth of Applicants' invention as claimed..

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). The claims rejected under §102(e) contain the elements of, inter alia, a *method of treating the underlying cause* the specified pathological conditions comprising administering to a subject a therapeutically effective amount of diacerein and/or rhein. Applicants respectfully submit that the teachings of DiNapoli do not contain the above-emphasized element.

Di Napoli fails to teach that the administration of diacerein or rhein to patients with PA, OA or RA will treat an underlying cause of PA, OA or RA. There is no disclosure in DiNapoli that the administration of diacerein or rhein to a patient will result in the *in vivo* inhibition of IL-1 and TNF-α production, the overproduction of which is an underlying cause of PA, OA and RA. The absence of this element from DiNapoli requires that this §102(e) rejection be withdrawn.

Rejections Under §103(a)

The Office Action rejected claims 1-14 as obvious over Martel-Pelletier et al. in view of Marcolongo et al. and Applicants' admissions on page 1 of the application. For the reasons set forth below and in the § 1.132 Declaration of Dr. Diego Provvedini filed with Applicants' previous response on September 17, 2002 (attached hereto for the examiner's convenience as Exh. A), Applicants respectfully traverse this rejection because Applicants' invention – i.e., the treatment with diacerein and/or rhein of an underlying pathological cause of any of the claimed genus of diseases – is nonobvious in light of the cited art.

Applicants first wish to respectfully point out that the Office Action's characterization of the disclosure of Martel-Pelletier et al. is incorrect. Martel-Pelletier et al. does not, as the Office Action states, disclose "a method of treating osteoarthritis (OA) employing diacerhein and its active metabolite rhein both of which are known to inhibit IL-1 beta synthesis and consequently have a beneficial effect on OA." The phrase "a method of treating OA" suggests that Martel-Pelletier et al. discloses the administration of diacerein and/or rhein to a human patient suffering from OA with a resultant beneficial outcome. This is not so. The reference quite clearly only discloses the *in vitro* (in glass) testing of diacerein on cultured cartilage tissue, which is different from administering diacerein to a human patient. The Abstract of Martel-Pelletier et al. states that the objective of the work is "to evaluate the *in vitro* effects of diacerhein . . . on [IL-1 and TNF-α] synthesis and expression . . . in human OA synovial membrane *explants*" (i.e., human cartilage tissue removed from a patient and placed in the artificial growth media of tissue culture). The authors draw no conclusion that diacerein or rhein will stop an underlying cause of OA – i.e., the destruction of cartilage tissue – when administered to humans. To the extent that the Office Action relies on the mischaracterization of Martel-Pelletier et al. in support of the § 103 rejection, the rejection is independently traversed.

The Marcolongo et al. reference adds little more than Martel-Pelletier et al. It does not teach the inventive contribution of the instant application: that diacerein and/or rhein can treat an *underlying cause* of a pathological condition characterized by increased IL-1 and/or TNF-α levels. At most, Marcolongo et al. teaches that a 100 mg dose of diacerein given daily for two months can reduce the *symptoms* of OA (pain, tenderness, etc.). There is no suggestion that this dose – or any dose – will stop or delay cartilage destruction in these patients.

Furthermore, Marcolongo et al. does not even mention IL-1 or TNF-α levels or their production, let alone reduction in their synthesis in patients after treatment with diacerein. In fact, the masking of symptoms can, potentially, be undesirable since it hides continuing cartilage degradation.

Applicants' cited "admissions" from page 1 of the application do not fill in the gaps in the teachings of the cited art. Applicants admit no more than that the diseases listed on page 1, lns. 10-14 are associated with increased IL-1 and/or TNF-α levels. There is no admission in the application that the prior art teaches a proper dosage of diacerein or rhein that can treat the underlying pathological causes of the enumerated diseases. The mere existence of an association between increased IL-1 and/or TNF-α levels and an enumerated disease would not teach one of ordinary skill in the art that an inhibitor of IL-1 and/or TNF-α will have an effect on an underlying pathological cause of the disease.

Furthermore, even when considered together, the combination of Martel-Pelletier et al. with Marcolongo et al. and Applicants' admissions on page 1 of the application is insufficient to support the obviousness rejection. An invention is not obvious merely because all of the claimed elements may be found collectively in the prior art; there must be something in the prior art to suggest the combination. *Key Pharms., Inc. v. Hercon Labs. Corp.*, 981 F. Supp 299, 316 (D. Del. 1997). Where claims are rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of whether the prior art would have revealed that in so practicing the invention of the claims, those of ordinary skill would have a reasonable expectation of success. *See In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). As the Declaration of Dr. Provvedini makes clear, one of ordinary skill in the art would not have been motivated to combine the *in vitro* results of

Martel-Pelletier et al., with Marcolongo's symptomatic treatment regimen and Applicants' admissions on page 1 and have a reasonable expectation of success that an underlying pathological cause of the disease would be ameliorated.

As Dr. Provvedini states, as a general matter it is not possible to link *in vitro* observations of the effectiveness of a drug with results observed *in vivo*. Those of ordinary skill in the art very often observe that several mechanisms are involved in the full expression of a pathologic condition in a patient. These same mechanisms are not necessarily present and/or involved in *in vitro* systems, due to many possible reasons such as the inadequacy of the model used, a lack of critical components and elements, or the insufficiency of the observation times.

Moreover, the field of art of Applicants' invention is particularly complex and highly unpredictable so that one of skill in the art could not reasonably conclude that the same effects observed *in vitro* will be obtained when a drug is administered *in vivo*. Dr. Provvedini identifies several of the variables that could cause an *in vitro* result to fail to correlate with the *in vivo* outcome. The lack of predictive value of the *in vitro* results of Martel-Pelletier et al. thus makes Applicants' invention nonobvious. The Office Action's combination of the cited art in its finding of obviousness without a showing of a reasonable expectation of success reduces the analysis to an impermissible "obvious to try" standard. *See Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1207-08, 18 U.S.P.Q.2d 1016, 1022 (Fed. Cir. 1991). Under similar circumstances, the Federal Circuit, its predecessor court, and the PTO Board of Appeals have refused to find an invention obvious. *See, e.g., In re Gangadharam*, 13 U.S.P.Q.2d 1568, 1569-70 (Fed. Cir. 1989) ("Simply because a drug gives positive results *in vitro*, it does not necessarily follow that there is a reasonable probability of success for therapeutic use of that drug *in vivo*.") (unpublished opinion); *In re Carroll*, 601 F.2d 1184, 1186-

87, 202 U.S.P.Q. 571, 572-73 (C.C.P.A. 1979); *Ex parte Mustard*, 143 U.S.P.Q. 305, 306 (PTO Bd. App. 1964) ("We are in agreement with appellant that in this complex and highly unpredictable art one cannot logically conclude that the same effects will be obtained [*in vivo*] as are realized in *in vitro* tests.").

Finally, a reference must be considered for *everything* that it teaches – including disclosures that teach away from the claimed invention, *In re Dow Chem Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988), and Martel-Pelletier et al. is no exception to this rule. Martel-Pelletier et al. concludes at p.760 that "Diacerhein is currently under investigation *in vivo* in patients with hip and knee OA *to explore its potential* structure modifying effects. The latter should yield useful information regarding the clinical relevance of this *in vitro* study." (Emphasis added.) As Dr. Provvedini states in his Declaration, the authors of the reference understood that the particular and unique complexity of this field would preclude any prediction that diacerein or rhein will stop an underlying cause of OA – *i.e.*, the destruction of cartilage tissue – when administered to humans based on the reported *in vitro* results. Indeed, this particular disclosure of Martel-Pelletier et al. is a teaching away from the claimed invention: the fact that the authors awaited the results of human trials before assessing the clinical relevance of the *in vitro* study indicates that they did not have a reasonable expectation of success that their *in vitro* model would necessarily correlate with the claimed clinical efficacy of stopping an underlying pathological cause of OA.

Therefore, Applicants respectfully submit that the § 103 rejection of claims 1-14 is inappropriate, and request that it be withdrawn.

§112, ¶1 Rejection of Claim 3 and
§132 Objection to Related Amendment to Disclosure

The Office Action rejected claim 3 under §112, ¶1, stating that the claim term "pulmonary fibrosis" was not specifically described in the specification. The Office Action also objected to the amendment adding "pulmonary fibrosis" to the specification as new matter under §132. Because the test for compliance with §112's written description requirement and for §132 new matter issues is essentially the same, Applicants will treat this rejection/objection as a single issue. *See Manual of Patent Examining and Procedure*, § 2163.01. For the reasons set forth below and in the Declaration of Dr. Provvedini submitted with Applicants' previous response on September 17, 2002 (attached hereto for the examiner's convenience as Exh. A), Applicants respectfully traverse this rejection and objection because "pulmonary fibrosis" is among those diseases suggested by the general language in the application to one of ordinary skill in the art, which is all that the law of written description requires.

The Office Action insists on maintaining the rejection of claim 3 because "pulmonary fibrosis" is not specifically described in the specification. Applicants respectfully submit that specific disclosure of "pulmonary fibrosis" in the specification as filed is not a requirement of the law of written description. *See In re Edwards*, 568 F.2d 1349, 1351-52, 196 U.S.P.Q. 465, 467 (C.C.P.A. 1978). All that the law requires is that "pulmonary fibrosis" be among those diseases suggested by the general language in the application to one of ordinary skill in the art. *See Forssmann v. Matsuo*, 23 U.S.P.Q.2d 1548, 1550 (Bd. Pat. App. Int. 1992). An inherent or implied disclosure of the claimed invention satisfies the written description standard if the skilled artisan would *recognize* from the disclosure that the applicant invented what is claimed. *See In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989); *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). Indeed

"inherency may be established either by the direct meaning of the language or by inferences drawn from the terms of the initial disclosure." *Standard Oil Co. v. Montedison, S.p.A.*, 494 F. Supp. 370, 384 (D. Del. 1980), *aff'd*, 664 F.2d 356 (3d Cir. 1981). A description of the genus of diseases covered by Applicants' claimed invention is therefore sufficient to support the claimed species of "pulmonary fibrosis" if the description contains "blaze marks" directing the skilled artisan to the species. *See In re Ruschig*, 379 F.2d 990, 994-95, 154 U.S.P.Q. 118, 122 (C.C.P.A. 1967); *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1326-27, 56 U.S.P.Q.2d 1481, 1486 (Fed. Cir. 2000).

In the Amendment submitted December 21, 2002, Applicants pointed to the numerous so-called blaze marks in the application that would lead one of skill in the art to include pulmonary fibrosis among the genus of claimed diseases. The Declaration of Dr. Provvedini made clear that one of ordinary skill in the art reading the application as filed would have understood that the genus of diseases covered by Applicants' claimed invention includes pulmonary fibrosis.

The Office Action also maintained the rejection on the grounds that pulmonary fibrosis is idiopathic in nature, i.e., that its cause is unknown or uncertain at best. The Office Action reasoned that because the claims recite a "method of treating an *underlying cause* of a pathological disorder," they could not possibly cover or envision covering pulmonary fibrosis, which allegedly has an unknown cause. Applicants respectfully submit that this basis of rejection of claim 3 is also incorrect and is grounded on a misunderstanding of the nature of the causes of pulmonary fibrosis and of Applicants' claimed invention.

First, by no means does the term "idiopathic pulmonary fibrosis" encompass all forms of pulmonary fibrosis. Indeed, idiopathic forms may be present in a variety of diseases.

See, e.g., Harrison's Principles of Internal Medicine, 14th Edition, 1997, at page 2051 (attached as Exh. B), identifying the existence of an "idiopathic atrophy of the adrenal gland." Furthermore, representative results of an internet search are attached as Exhibit C, confirming that idiopathic forms of diseases are present in practically all organ and tissue systems. Thus, "idiopathic" does not pertain to the entire group of diseases known as "pulmonary fibrosis," but only to a certain subgroup within this group. Notably, Applicants claim a "method of treating an *underlying cause* of a pathological condition," which, by its own terms, would exclude those pathological conditions for which all causes – both originating and intervening – are unknown.

Second, even when a disease is idiopathic, some of its manifestations can still be treated by directing the treatment to known intervening causes of the disease, even if the originating cause of the disease is unknown. Accordingly, Applicants' claim 3 reads " ... a method of treating *an* underlying cause of a pathological condition ..." which is very different from " ... treating *the* underlying cause ..." Indeed, a web page on the Pulmonary Fibrosis Foundation's own website discusses several possible therapeutic strategies for the treatment of idiopathic pulmonary fibrosis (attached as Exh. D). This same web page also remarks upon the "series of events" (the intervening causes) leading to lung inflammation that follow the triggering (the unknown originating cause) of idiopathic pulmonary fibrosis. This evidence further indicates that potential treatments can be proposed and claimed even for the idiopathic form of pulmonary fibrosis, and that this treatment can be directed, as Applicants claim, at the intervening causes of the disease, i.e., the increase in IL-1 and/or TNF-α levels. In addition, the Pulmonary Fibrosis Foundation text cited in the Office Action begins with the words: "Pulmonary Fibrosis is a disease for which, *in most cases*, there is no known cure..." In the

emphasized text lies the interest of proposing new therapeutic measures that may be useful in the remaining cases.

Therefore, Applicants respectfully submit that the § 112, ¶ 1 rejection of claim 3 and the corresponding objection to the amendment to the specification are inappropriate, and request that they be withdrawn.

Restriction of Claims 15-23 and Constructive Election Of Claims 1-14

The Office Action subjected to restriction newly submitted claims 15-23 and withdraw them from consideration as being constructively elected under 37 C.F.R. § 1.145 because claims 15-23 were directed to an invention that is independent or distinct from the invention in claims 1-14. The basis for the restriction was that: 1) claims 15-23 require the employment of two different groups of actives, whereas claims 1-14 require the employment of only one pharmaceutically active agent; and 2) claims 15-23 have a different mode of operation than claims 1-14. Applicants believe that a Restriction Requirement is inappropriate in this case because the inventions of claims 1-14 and of claims 15-23 are not independent and distinct.

First, the Office Action apparently misreads claims 19 and 22 to recite the administration of two different groups of actives, which the claims do not. Claims 19 and 22 merely add to independent claims 1 and 11, respectively, the limitation that the need for surgery to treat the pathological condition is avoided, delayed or reduced by the administration of diacerein or rhein. The added limitation only further characterizes the effect of the treatment, *i.e.*, beyond treating an underlying cause of the pathological condition as recited by claims 1 and 11. Therefore, there is no different mode of operation of claims 19 and 22 compared to claims 1-14. For these reasons, claims 19 and 22 should not be subjected to restriction.

Second, the second active agent co-administered with diacerein or rhein in claims 15-18, 20-21 and 23 does not affect the fundamental mode of operation of claims 1-14, which is the treatment of an underlying cause of a claimed pathological condition. The second active merely provides either: 1) symptomatic relief in addition to treatment of the underlying cause of the pathological condition (claims 15 and 21); or 2) enhances or supplements the effect of diacerein or rhein (claims 16-18, 20 and 23). The addition of such active agents would not require a separate classification in the PTO patent classification system; it would not give the claims a separate status in the art; and it would not require a separate field of search. For these reasons, claims 15-18, 20-21 and 23 should not be subjected to restriction.

CONCLUSION

Applicants submit that the above Remarks are sufficient to overcome the outstanding rejections of the claims and the restriction requirement. Consequently, Applicants submit that the claims are now in a condition for allowance and respectfully request that they be allowed to go to issuance.

Respectfully submitted,

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Dated: February 4, 2003